

previously. A girl born later had died from tuberculous peritonitis, but a boy aged 5 was alive, though frail looking.

The photograph taken shortly after the expulsion shows the cords of the twins inserted at opposite points in the placenta, the distension of the cord of the foetus and the sharp twist at the navel, and the wall of the abdomen wrinkled. Comparison of the bodies shows the skin of the scalp and body more lax than the skin and scalp of the other foetus, but the skins of both are seen in peeling stage. The appearances are consistent with the story of the mother, and it would hardly be expected that decomposition would be further advanced at the end of 11 days after cessation of movement in utero. If, therefore, the putrefactive changes were not widely different in the twins and were only a degree more in one than in the other, and one had a twisted cord while the other had not, it seems reasonable to infer that the foetus with the obliterated cord died first, and that the death of the other followed not long after, say, seven or eight days or even less.

Tyler Smith and indeed all writers attribute torsion to the movements of the foetus, and in the case of twins it is fair to suppose that there might be less space for movement. The exact position of the twist would depend upon intra-uterine conditions impossible to formulate. The cord may get an obliterating twist close to the body of the foetus, or it may become equally obliterated by a twist somewhere in its course away from the fixed points at the placenta and navel.

The silence of text-books on torsion of the cord—with the exception of those authors quoted—suggests that either the question is too trivial for mention, or that the cases of death from intra-uterine torsion are few and far between. Then comes the statement that torsion is a post-mortem occurrence. That this may be so in many cases no one would question, but I do not consider that the case now recorded belongs to that class. Possibly few cases are on record where twin foetuses grew equally for a certain time, and then one dying with a twisted cord caused the other to die also. I had a few years ago a twin birth, one child living and apparently healthy, whereas the small dead foetus was quite black and shrunken. Syphilis was the reason, because the living child was the object of much anxiety and thrived well on grey powder. The twins in the case recorded were not examined post mortem, and the appearances are those seen in the photograph.

Bibliography.—Transactions of the Obstetrical Society, vol. x., p. 94: "Dr. Rasch exhibited a foetus and placenta (5 months?) in which the cord was obliterated by twisting. Close to the navel of the foetus the funis had the appearance of firmly twisted, thin cord of the thickness of a crow quill." Transactions of the Obstetrical Society, vol. xii., p. 51: "Dr. Westmacott exhibited a remarkable specimen of 'corkscrew funis' (no details given). Transactions of the Obstetrical Society, vol. xxxi., p. 164: "Dr. M. Handfield-Jones showed specimens of curious twistings of the cords around foetal limbs lashing them together, the funis in one case being dragged out into a thin, ribbed-like ligature, and it was a matter for surprise how the circulation could possibly have been carried out through such a flattened structure." Tarnier et Budin, vol. ii., p. 362: "The labours of Martin, of Ruge, and of Schauta show that in the great majority of cases it is not the exaggerated torsion of the cord which has brought about the death of the foetus." The quotation from Hirst already alluded to seems somewhat too sweeping in view of the reference to Tarnier and Budin.

Carlisle.

THE ACTION OF THE PRODUCTS OF HOMOGENEOUS FETAL AUTOLYSIS ON MALIGNANT TUMOURS IN MAN.

PRELIMINARY NOTE.

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THE study of the biology of embryonic and neoplastic inoculations, which I undertook some time ago, has afforded me various results on which are founded the researches here detailed.

1. The observation of the extreme rarity of spontaneous malignant tumours in young rats. This fact recalls the absence, or the very exceptional occurrence, of simple neoplasms or specific tumours, as epitheliomas and sarcomas, in the newly born and young subjects, and leads one to

believe that, in the early epochs of life, the factors necessary for the genesis of malignant tumours do not exist.¹

2. The fact of the noteworthy and frequent resistance to the inoculation of neoplasms which rats acquire by previous injections of embryonic or foetal tissues. Such a fact suggests the existence of some substances contained in, or originating from, the inoculated foetal tissues which, on diffusion, render the subject immune to subsequent attempt to reproduce malignant growths.

3. The demonstration that homogeneous embryonic or foetal tissues, when subjected to autolysis, by hypodermic injection or by local application, bring about the involution of the inoculated neoplastic elements, which always reproduce themselves and prove fatal. This fact strengthens a belief in the existence of substances which are generated by the special tissues during the process of autolysis, which when injected into the organism act on tumours in a way similar to that brought about by the preventive injection of embryonic or foetal emulsion.

Accordingly, guided by these facts, I have deemed it well to examine the effect of homogeneous products of foetal autolysis in cases of malignant tumours in the human subject. The observations, begun early in September, 1909, and continued without interruption, have been all conducted on inoperable cases, of which only 7 had received no surgical treatment, although seen by the ablest and most daring surgeons, when no operation was possible; 29 had been operated upon, even repeatedly, including recurrent cases and several with multiple and voluminous metastases. In each case the histological diagnosis was confirmed without exception, and the clinical evolution was followed up, both anatomically and microscopically, by means of the excision of small portions, repeated even eight times.

The number of cases submitted to the injections was 36. Of these, 14 stopped the treatment early by their own desire for various personal reasons, having received from three to ten injections. From the other 22 cases we must subtract four, in whom the treatment has been only recently begun, and, although in three of these the first subjective and objective symptoms of improvement have begun, one cannot as yet depend on any result.

There thus remain for consideration 18 patients affected by malignant tumours, varying in substance and position, who have followed up the treatment with regularity and perseverance. Of these, eight have derived no marked benefit, except in a few cases some delay in the progress of the tumour or an initial improvement of the general condition, but only to be followed by a progressive deterioration, so that in three of these cases a fatal result occurred, an inevitable event in inoperable tumours, and considered as imminent in all the cases confided to me.

As for the other ten cases, the beneficial effects are evident; and while in five cases the treatment is still proceeding, because the tumours have neither disappeared nor become modified in structure, in the other five cases the neoplastic tissues have completely disappeared, or in the residual tissue repeated excisions have demonstrated the complete transition of neoplastic into sclerotic connective tissue. Of these, three presented metastases which had degenerated sooner than the primary tumour in a manner analogous to that observed in four other cases in which the glandular metastases have now disappeared, although the original tumour, or its reproduction, still exists, more or less modified.

In the five cases in which an accurate and repeated histological examination of various portions of the neoplasms has abundantly proved the benefit of the treatment, we have to deal with three cancers of the breast, with multiple metastases, one cancer of the lower end of the rectum, and one adeno-carcinoma of the thyroid. The first case treated is omitted from this group, the only one in which a preliminary excision was not made. This case was diagnosed as epithelioma of the soft palate, with cervical metastasis. As soon as the injections were begun the various manifestations disappeared, and that quickly. In waiting for the result the pieces excised, examined when the involution was well advanced, yielded the typical histological appearance, by this time found to be constant, of a change of formation now no more recognisable by the finest methods; hence the doubt as to its nature.

In all the cases the process of cure was similar; the same

¹ THE LANCET, Oct. 15th, 1910, p. 1151.

leading phases were gone through, and the same definite structure attained. The local treatment by injection into the parenchyma provoked hæmorrhagic, necrobiotic, or necrotic areas around, which were rather more numerous and more extensive than those occasioned by the remote injections, of which the main feature was cytotoxicity with a moderate degree of substitutive connective tissue.

Except for this difference, constant microscopic results were successively found—viz., a diffuse cytotoxicity of the neoplastic cells, gradually more pronounced till the morphological entity was lost, and the elements had broken up; intense infiltration, especially among the smaller cells, more marked around the vessels of various sizes; the penetration of numerous phagocytes, small and great, and of cell plasma; the active proliferation of connective and vascular tissues, invading, in fact, the whole region, some with giant cells; the transformation of the tumour substance into adult connective tissue, both fibrillary and sclerotic, with a cessation, briefly, of all reaction and production of infiltration and multiplication.

In some cases there was intense vascular stimulation of a lymphatic type; whence came a turgidity of the neoplastic tissues, and a marked increase of volume, with a change of consistency, amounting to clear fluctuation. By aspiration, in such cases, a limpid lemon-yellow liquid is obtained, having the characteristics of a transudation, containing whitish particles in suspension.

After the fluid or the infiltration had been absorbed, the substitution of tissue already affected by degeneration and by cytotoxicity happens as usual, which process, in its complexity, forms a picture perfectly analogous to that described by me in the case of malignant sarcomas in rats treated by homogeneous fetal "autolysates"; it is a condition, therefore, comparable to that of sarcomas and epitheliomas engrafted on rats, previously immunised by embryonic or foetal inoculation. From which circumstance, in short, there is a resemblance to the spontaneous evolution displayed by tumours only slightly virulent, and to the embryonic graftings in the second period of the cycle—viz., in the state of regression and disappearance.

There is no need to insist in this short notice on the importance of this uniformity of course and of results, a proof of the existence of physio-pathological phenomena, explicable by general laws, revealing themselves with the greater intensity and diffusion according to the measure and coöperation of complex factors.

One must here pause to call attention to the analogy of the structural characters, as above explained, with those noted by various authors, especially of the school of Orth, in the very rare cases of spontaneous involution of tumours in the human subject, in which may be found "zones," more or less restricted or extensive, which are affected, as I believe, by products of limited autogenetic neoplastic cytotoxicity, due to partial breaking down from defective nutrition or from the formation of hæmorrhagic patches. Generally speaking, one meets also in such cases with the same phenomena and the same conditions, by means of which the organism in its various changes, with only its inherent powers of cure or aided by treatment, succeeds in substituting a pathological tissue, structurally and biologically hurtful, by a common cicatricial tissue, biologically innocent.

During the treatment I have succeeded in making some remarkable observations, and have studied the anatomy, histology, and pathology of the process. In the first place, I have been able to prove that the modifications in volume are not proportionate to those of structure, so much so, that the criterion of the dimensions or of the consistency is not always a safe guide to the estimate of the therapeutic effects. In fact, in some cases there are notable differences relating specially to the original size of the neoplasm, as also to the time occupied in the cure and its methods. For example, the cases of metastasis, which even if relatively large, may not assume excessive dimensions, and are often decidedly influenced by the products of autolysis, may disappear without leaving a trace. Voluminous tumours, on the other hand, especially if treated locally, require much time for their change of substance, particularly by reason of the formation, by direct and intense action, of hæmorrhagic, necrobiotic, or necrotic patches around which the process of disintegration is long and slow, and an excess of connective tissue is formed.

A typical example of such a course was displayed by a large cancer of the breast with metastasis, in which, after a

preliminary course of general treatment, a slight diminution having taken place, an excision was performed in March, 1910. The microscopic examination showed the existence of an alveolar carcinoma, with zones of neoplastic cytotoxicity, infiltration of leucocytes, and proliferation of connective tissue. Owing to the bulk of the neoplasm, and in order to act more directly upon it, local injections were undertaken. In May the dimensions seemed increased, on which account the previously existing metastasis, above and below the clavicle, having disappeared, an operation was decided upon. The breast having been removed and the axilla cleared out, it was found that both the main mass of the tumour and the small axillary swellings were extensively composed of abundant sclerotic connective tissue, in which here and there were found the evidence of spaces with contained cells in such a condition of cytotoxicity as to be unrecognisable in their minute characters, having the appearance of coloured soil, suspended *in vacuo*, only here and there outlined by fine lines like cellular membranes. Although the operation could not be considered as radical, from examination of the piece removed, and although from the extensive destruction of the parts it was not possible to suture, at the first, the whole line of incision, by continuing the injections a regular granulation and formation of epithelium was obtained without proliferation of the neoplastic elements, as proved by histological examination.

Another case also noteworthy was the adeno-carcinoma of the thyroid, which at first by general treatment disappeared, apparently by cytotoxicity, and a slight production of fibroplastic material, so much so that the cure was somewhat prematurely stopped, no trace being found by palpation. In the recurrence local treatment led, by the usual stages, to the subsidence of the neoplastic tissue, and to its replacement by a quantity of sclerotic connective tissue.

Another remarkable observation proves the inherent differences in the methods of cure. In fact, while normal doses, injected under the skin in the most varied parts of the body, do not produce local or general phenomena of special interest, or, at least, in some cases treated by rather strong doses, only slight redness, temporary oedema, and a momentary rise of temperature, merely a fraction of a degree, the same doses, on the other hand, provoke intense and exaggerated phenomena of the same kind when injected into the neoplastic tissues. Individuals who have had several courses of ten doses each of general injections without disturbance, when the same doses are given into the parenchyma of the neoplasm readily showed a reaction, with fever up to 39° or 40° C., with rigors and headache, followed in a few hours by a cessation of such symptoms and profuse sweating. In a few days a redness appears over the neoplasm, at times fairly extensive, with swelling and hardness. If the injections be now continued, sometimes the extent of the parts so affected increases, distension and fluctuation are felt, due to the formation of the clear lemon-coloured fluid formerly referred to, which may be at times blood-stained, as the result of aspiration, and may rapidly re-accumulate and persist. It is well in such cases to make an incision and give vent to the fluid, which goes on flowing several days, and gives place to granulation and cicatrization of the wound, and to the substitution of the neoplastic tissues. This process is rendered difficult, at first, by the distension and infiltration obstructing the more remote superficial lymph supplies, on which the newly formed cicatrix chiefly depends. In four cases at an advanced stage of the treatment a free incision of the neoplastic parenchyma, treated by simple dressing, resulted in a good cicatrix by granulation.

The difference in the general effects of the two methods of treatment was exhibited, with a variable frequency, by all the patients, to whom they were applied indifferently. And yet, while awaiting the report of the histological examination in order to confirm the clinical diagnosis, the latter (diagnosis) is assisted and anticipated by the fact that the strongest innocuous subcutaneous dose, at once and in a marked degree, gave rise to the above group of symptoms.

To elucidate the origin of this fact I experimented on rats and guinea-pigs, injecting varied doses of neoplastic and foetal autolysates, and of fluid taken by aspiration from effusions formed locally by the treatment. The examination of symptoms, the result of necropsies, the microscopical changes, which were common to all the substances injected, have led me to a definite conclusion.

The principal lesions of the hyperæmic and hæmorrhagic

type, subsequently degenerative, which are only obtained by doses equivalent, relatively to the weight of the body, to 400, 700, or even 900 times that usually employed in the human body, are found in the excretory organs, the liver and kidneys, and in the internal protective secretory organs, as the pituitary and thyroid glands, and the suprarenal capsules, these last organs, indeed, being those most frequently and most seriously attacked by hæmorrhages. Such an anatomical and pathological condition, both naked-eye and microscopic, has been detected also, in the case of doses incapable of causing it in healthy guinea-pigs, in four which were accidentally found to be tuberculous at the necropsy, while the others of the same group showed no special alteration.

I have, therefore, come to regard the transitory group of symptoms as a slight, but complex, toxic phenomenon, favoured at first, in the case of local injections, by peculiar structural conditions, especially as regards the vascularity of the surrounding parts and the friability of the blood-vessels, leading to a more abundant and more rapid absorption by the blood; and, in the second place, increased by the excessive action due to the contemporaneous penetration of the products of cytolysis of the neoplasm, if such have already been formed. Such an explanation is confirmed by the fact that, on the disappearance of the neoplastic tissue, the effects of the local injections in no way differ from those of the general treatment.

The mechanism of the action of the autolysates requires diligent study before it can be defined with certainty and accuracy.

On a hypothesis based on somewhat similar work I have endeavoured to prove that, if we have to deal with an enzymatic process, it is most decidedly due to the combined action of all the enzymatic powers of the foetal organism. I have, therefore, made numerous tests on films of the serum of coagulated blood, which were easily dissolved by even weak solutions of trypsin. The autolytic products from five sections of tumours of rats and from seven neoplasms from the human subject have afforded me on two occasions, and only one quite distinctly, zones of digestion. But out of 11 foetal autolysates tested, differing as to the age of the foetus and as to the stage of the experiment, none has dissolved the albumin subjected to the test. In the same way the fluid aspirated from the fluctuating parts produced by local treatment has given a negative result in two cases and a positive result in one, which was not trustworthy by reason of contamination of the material.

These tests on coagulated albumin and on extra-corporeal tissues are not proofs of the enzymatic property of foetal autolysates. More numerous and more delicate researches are certainly necessary for such conclusions. It seems to me, however, fair to form some conclusion on the direct and elective actions of these autolysates.

The direct action in the living subject between the products of foetal autolysis and neoplastic cells is proved by the following considerations:—

(a) The failure to immunise rats against the inoculation of homogeneous sarcoma, after preventive treatment, even much prolonged; their receptivity was not modified by the progressively increased injections of autolysates.

(b) There was no effect on the pulp of sarcoma produced by the serum of rats prepared with injections of homogeneous foetal autolysates; the pulp thus employed acted like fresh pulp.

(c) The transitory resistance acquired by rats against tumours by preliminary inoculations of embryonic or foetal tissues; this immunity ceases after a short time.

(d) The fact that if the treatment be suspended when no lumps are to be felt exceptionally a case may again develop the neoplasm from the residual elements, which are not apparently under the influence of hurtful substances produced by the organism for some time after the treatment.

(e) The readiness with which the changes in the parenchyma of the neoplasm are produced by local injections before the formation of antitoxins is possible.

(f) The persistence of the therapeutic action with local and general reaction, after even a fairly long period of treatment and numerous injections; there is, therefore, no evidence of immunisation.

The elective action is proved by the effects obtained by general injections in rats and in the human subject—e.g., in the case of a cancer of the rectum and in the early treatment

of the adeno-carcinoma of the thyroid, as also in six out of seven cases of relapsing metastasis—by the fact that in the normal tissues there is no evident reaction; in fact, only during a few days a slight hyperæmia is met with at the point of injection, and sometimes a small zone adherent to the subcutaneous tissue which shows under the microscope a very fine structure with a fibrinous network and a few scattered leucocytes, whereas, in contrast to this condition, in the tissues under treatment the changes already described are found; by the clearly marked lesions which, soon after the injection into the substance of the neoplasm, appear along the line of puncture, such as are not found in normal tissues.

This double proof of the direct and elective action of the autolysates on the effect of the treatment points to the relation between the dose of the substance injected and the volume of the tumour. In practice it happens that, as we must not exceed certain fixed doses, if the tumours be unusually large the autolysates injected at a distance destroy a less amount of the neoplastic tissues than that formed in the same period of time. It is, accordingly, only possible to obtain a delay in the morbid process, which will become less and less important the more the disproportion will increase between the continued employment of the maximum dose adopted and the progressive increase of the volume of the tumour. In such cases one must have recourse to the most energetic local treatment, taking care in the case of marked cedema or evident effusions to aspirate, or in other ways to get rid of the products of neoplastic cytolysis.

Moreover, in such conditions of volume and rapid growth of the neoplasm, and of action of the autolysate both limited and proportionate to its dose, it increases the chance of success in destroying the neoplasm and in restoring the patient's health to excise or destroy freely in order to act on any possible residual cells, and on the metastasis, only by general treatment. Individuals with inoperable tumours can thus undergo the treatment without the risks due to the absorption of toxic products, especially such as are of neoplastic origin, and will exhibit, as early signs of improvement, marked modifications of their general condition, and especially of the blood.

This varied effect of one and the same treatment has suggested the hypothesis brought forward by Bagnami at a recent meeting of the Academy of Medicine of Rome, of the complexity of the substances contained in foetal autolysates. Of such one group may have a stimulating action on the healthy tissues, and especially on the hæmopoietic organs; and another group may be responsible for the cytolytic action on the neoplastic tissues. One may also admit the existence of a single series of active principles, which would act successfully, in different ways, according to whether they had to deal with normal cellular elements or neoplastic elements; hence a double favourable result.

The same mechanism of elective cytolytic action, without which the tumour would not otherwise disappear, forms a contra-indication to the treatment in cases with cachexia, in which, by all means, if a cure be undertaken, we must try to prevent the increase of intoxication. The toxic action inherent to the constitution and biology of malignant tumours discourages the use of their autolysates in experimental therapeutics, because there would result an excessive action, more intense and more serious than with other methods. It is necessary, in fact, to employ homogeneous embryonic or foetal autolysates. In my cases I have employed embryos and foetuses of from two to six months of intra-uterine life, adopting the products of *foetal* autolysis more frequently and for a longer period.

It cannot be denied that autolysates from adult organisms may possess a similar action, although it must be reckoned less efficacious, to judge from the less potency and the less frequency with which they confer an immunity against tumours as appears from numerous experiments. It seems to be rather more difficult to admit the same beneficial power in the case of heterogeneous autolysates, especially as on the basis of modern researches on tumours the laws of biological selection appear to be distinctly confirmed under the most varied aspects.

The homogeneous foetal autolysates are prepared by ordinary methods, observing the strictest rules of asepsis. The fragments, or the pabulum, of the foetus are placed in a physiological solution, of an average strength of 1 grm. to 20 cgrm., a suitable quantity of thymol or phenic acid being

added, and covered by a layer of sterilised oil or toluol. The mixture remains in the incubator at 37° C. for about two months, and prior to use its sterility is tested.

The injections vary in dose from 2 to 3 c.c. twice to four times a week, according to the patient's age, condition, individual tolerance, the bulk of the tumour, the seat of the injection, and the specific gravity of the autolysates, which latter ought to be, at the moment of their employment, a homogeneous emulsion, and not a clear superjacent mixture. The treatment extends to a variable number of months, according to the local and general conditions.

While in this article I limit myself to describe the action of autolysates on malignant tumours in the human subject, and to make a general statement as to their therapeutic effect, I have at the same time arrived at conclusions of some statistical value, which prove the exactitude of all I have stated, but do not admit the conception of a statistical comparison. Such could only be made after a study of numerous cases, and only when time, rather than repeated excisions and numerous histological controls, shall have proved that even the last neoplastic cells have been destroyed, and consequently all danger of recurrence eliminated. All the more the fact remains that, without proof of an immunisation, there remains in every individual the possibility of the development of blastomic cells, on which account, if all the conditions requisite for the formation of a neoplasm be again present, the subject in question is always liable to, and helpless against, such a contingency.

The observations, however, made on both men and animals have so far proved that, if the treatment be persisted in for some time after its evolution and disappearance, the tumour does not recur. And if, as an exception, a case in the human subject relapse on account of a premature suspension of the injections, if the latter be resumed their effects are again manifest. Time only will permit of the collective study of cases submitted to this treatment in more favourable conditions than were hitherto possible, when one may be able to supervise and study the process in every detail, with fresh material, and, by this original method, deal with inoperable cases of voluminous tumours and their metastases.

Finally, I desire to add that I have indicated the method and its results in detail, because, as may be readily understood, in relating the clinical researches, which are indispensable for a fair conclusion, one has to bear in mind the relative number of cases treated and the long time of trial necessary for a satisfactory judgment.

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Rome.

UNIVERSITY OF LONDON.—The Graham scholarship in pathology of the value of £200 a year, tenable at University College Hospital Medical School, was awarded for the sessions 1911-12 and 1912-13 to Mr. H. G. Butterfield, M.A., B.M., B.Ch., of Wadham College, Oxford, and University College Hospital.—The Brown Animal Sanatory Institution Committee have appointed Sir William Church as their chairman, and the members of the Senate Committee have appointed as chairman Dr. Frederick Taylor.—In response to the appeal to raise £15,000 as a building fund for the Galton Laboratory for National Eugenics, sums amounting to a total of £2260 have already been given, promised, or promised conditionally on the buildings being commenced within two years.

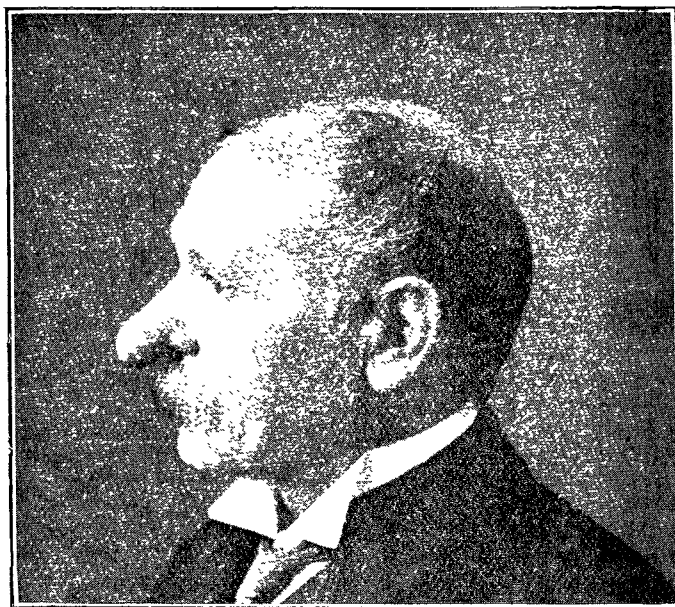
Clinical Notes: MEDICAL, SURGICAL, OBSTETRICAL, AND THERAPEUTICAL.

THE RESULTS OF OPERATION IN A CASE OF HAMMER NOSE.

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As the effects of operative interference in cases of rhinophyma, or hammer nose, are not often seen the accompanying photographs of a case of this kind may be of interest. This distressing condition first appeared when the patient was

FIG. 1.



26 years of age, and grew steadily worse, making his life a misery and his nose a constant source of annoyance to himself on account of the attention and ridicule it evoked.

The patient at the time of operation was 64 years of age. He was, and had always been, temperate. With

FIG. 2.



the exception of a faint aortic bruit he was a healthy man and had had no serious illness. Under chloroform anæsthesia the whole of the superfluous tissue was removed